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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APR - 4 1997

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Copper octanoate *(NEU 1140 F)*. Review of Acute Toxicity Studies

P. C. CODE: 023306
SUBMISSION NO.: S511757 & S512579
DP BARCODE: D230195 & D230567
MRID NUMBER: 43947504, 43947505, 43970201, 43947506, 43947507 & 44116101

FROM: Sanjivani Diwan, Ph.D. Sanjivani Diwan 3/17/97
Review Section I, Toxicology Branch II
Health Effects Division (7509C)

TO: Cynthia Giles-Parker/James Stone/PM-22
Registration Division (7505C)

THROUGH: Jess Rowland, M.S., Acting Head 3/17/97
Review Section I, Toxicology Branch II
Health Effects Division (7509C)

and

Yiannakis M. Ioannou, Ph.D., Acting Chief 3/26/97
Toxicology Branch II
Health Effects Division (7509C)

Registrant: W. Neudorff GmbH KG, Germany

Action Requested: Toxicology Branch II has been asked to review a series of acute toxicity studies submitted by W. Neudorff GmbH KG, Germany to support registration of Copper octanoate (10% formulation)

Recommendation: Toxicology Branch II has determined that the reviewed acute toxicity studies on Copper octanoate are Acceptable and satisfy their respective guideline requirements (81-1 thru 81-6).

Review of Toxicology Data

Acute Toxicity Studies (Guideline §81-1, 81-2, 81-4, 81-5 and 81-6; MRID # 43947504, 43947505, 43970201, 43947506, 43947507 & 44116101):

- Oral LD_{50} - Rat (MRID No.: 43947504)

  Male and female (5/sex) Wistar Crl: (WI) BR rats were orally administered single doses of undiluted test material at dose level of 2000 mg/kg.

  The estimated acute oral LD_{50} for Copper octanoate (10% copper fatty acids) was >2,000 mg/kg for the sexes combined.

  Toxicity Category III; the study is classified as Acceptable

- Dermal LD_{50} - Rat (MRID No.: 43947505)

  Male and female (5/sex) Wistar Crl: (WI) BR rats received dermal application of undiluted test material at a dose of 2,000 mg/kg (Limit dose) for 24 hours.

  The acute dermal LD_{50} for Copper octanoate (10% copper fatty acid) in male and female rats was greater than 2,000 mg/kg.

  Toxicity Category III; the study is classified as Acceptable

- Inhalation LC_{50} - Rat (MRID No.: 43970201)

  Groups of five male amd five female Sprague-Dawley rats were exposed to aerosol concentration of 0.38 mg/L NEU 1140 F for four hours.

  The acute inhalation LC_{50} was >0.38 mg/L (the highest achievable concentration) in both sexes of rats.

  Toxicity Category III; the study is classified as Acceptable.

- Primary Eye Irritation - Rabbit (MRID No.: 43947506)

  Approx. 0.1 g of test material was instilled into the conjunctival sac of one eye of three male New Zealand White rabbits. The other eye served as an untreated

control.

The study demonstrated that NEI 1140 F produces transient ocular irritation in rabbits.

Toxicity Category IV; the study is classified as Acceptable

- Primary Skin Irritation - Rabbit (MRID No.: 43947507)

0.5 g of test material moistened with 0.5 ml of 0.5% distilled water was applied to a clipped skin area of three male New Zealand White rabbits for four hours. The study demonstrated that Copper octanoate is non-irritating to the rabbit skin.

Toxicity Category IV; the study is classified as Acceptable.

- Dermal Sensitization - Guinea Pigs (MRID No.: 44116101)

In a Maximization Test, twenty female Himalayan albino guinea pigs received three intradermal injections of 0.5% NEU 1140 F in distilled water and an epidermal application of undiluted test material during induction phase. During challenge phase, a topical application of 50% test substance concentration in distilled water was administered to animals.

The positive control group received 5% alpha-hexylcinnamicaldehyde in distilled water and undiluted (alpha-HCA) during induction phase and 50% alpha-HCA during challenge phase.

NEU 1140 F is a non-sensitizer of skin in female guinea pigs.

The study is classified as Acceptable.

Copper Octanoate Acute Oral Toxicity (§81-1)

Reviewed by: Sanjivani B. Diwan, Ph.D. Sanjivani B. Diwan, Date: 2/25/97
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Alan C. Levy, Ph.D. Alan C. Levy, Date 2/25/97
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Acute Oral Toxicity - Rats OPPTS 870.1100 [§81-1]
DP BARCODE: D230195 P. C. CODE: 023306	SUBMISSION NO.: S511757 MRID NUMBER: 43947504
TEST MATERIAL (PURITY):	Copper Octanoate (10% copper fatty acids)
SYNONYM:	NEU1140F
CITATION:	Pels Rijcken W.R. 1995. Assessment of Acute Oral Toxicity with NEU 1140 F in the Rat. NOTOX Hambakenwetering 3, 5203 DL's-Hertogenbosch, Netherlands; NOTOX Project 154801. September 27, 1995
SPONSOR:	Neudorff GmbH KG, D-31860 Emmerthal, Germany

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID # 43947504), groups of five male and five female Wistar Crl: (WI) BR rats received single oral dose of NEU 1140 F at dose level of 2000 mg/kg. **Based on the acute oral LD_{50} of >2,000 mg/kg (Limit dose) for both sexes, NEU 1140 F (10% Copper fatty acids) was placed in Toxicity Category III.**

This study is classified as **Acceptable** and **satisfies** the requirements (81-1) for an acute oral toxicity study in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided. No Flagging statement was provided.

I. MATERIALS

A. Test Material

Chemical Name: Copper Octanoate
Synonym: NEU 1140 F
Purity: 10% copper fatty acids
Batch Number: 03/03
Description: Turquoise liquid
Storage Conditions: At room temperature in the dark

The dosing solution was administered undiluted. Dose-volumes were determined based on the body weight of the individual animal and administered by gavage at a dose volume of 1.90 ml/kg. Food was withheld prior to dosing.

B. Test Animals

Species: Rat
Strain: Wistar Crl:(WI) BR
Source: Charles River, Germany
Age: Approx. 7 weeks
Weight before dosing: Males - 225 to 249 g; Females - 181 to 192 g
Housing: Five rats of same sex per polycarbonate cage
Environmental Conditions: Temperature: 21°C
Relative Humidity: 50%
Photoperiod: 12 hours light/dark
Air Changes: 15/hour
Food and Water: Standard Pelleted Animal diet (Carfil quality BVBA, Oud-Turnhout, Belgium) and water *ad libitum*
Acclimation Period: Five days

II. STUDY DESIGN AND METHODS:

No rational for the selection of dose level was provided.
For the main study, the animals were fasted overnight prior to dosing. Each animal received a single dose of the test solution on a g/kg body weight basis. Five male and five female rats were dosed with test solution (1.91 ml volume/kg b.w.) at 2,000 mg/kg via gavage. The animals were observed for clinical signs of toxicity at least once daily and for mortality twice daily throughout 15 days of observation period. Body weights were recorded on the day prior to dosing as well as at 8 and 15 days post-dosing. At the end of the observation period, all animals were sacrificed and necropsied. No statistical

II. RESULTS

There were no mortalities observed from day 1-15 after dosing. No clinical signs were observed until 15 days post-dosing. The body weights were unaffected. There were no lesions observed on gross necropsy of the animals sacrificed at study termination with the exception of reduced size of testes in one male which was considered to be incidental. The estimated acute oral LD_{50} was >2,000 mg/kg for males and females combined.

III. CONCLUSIONS

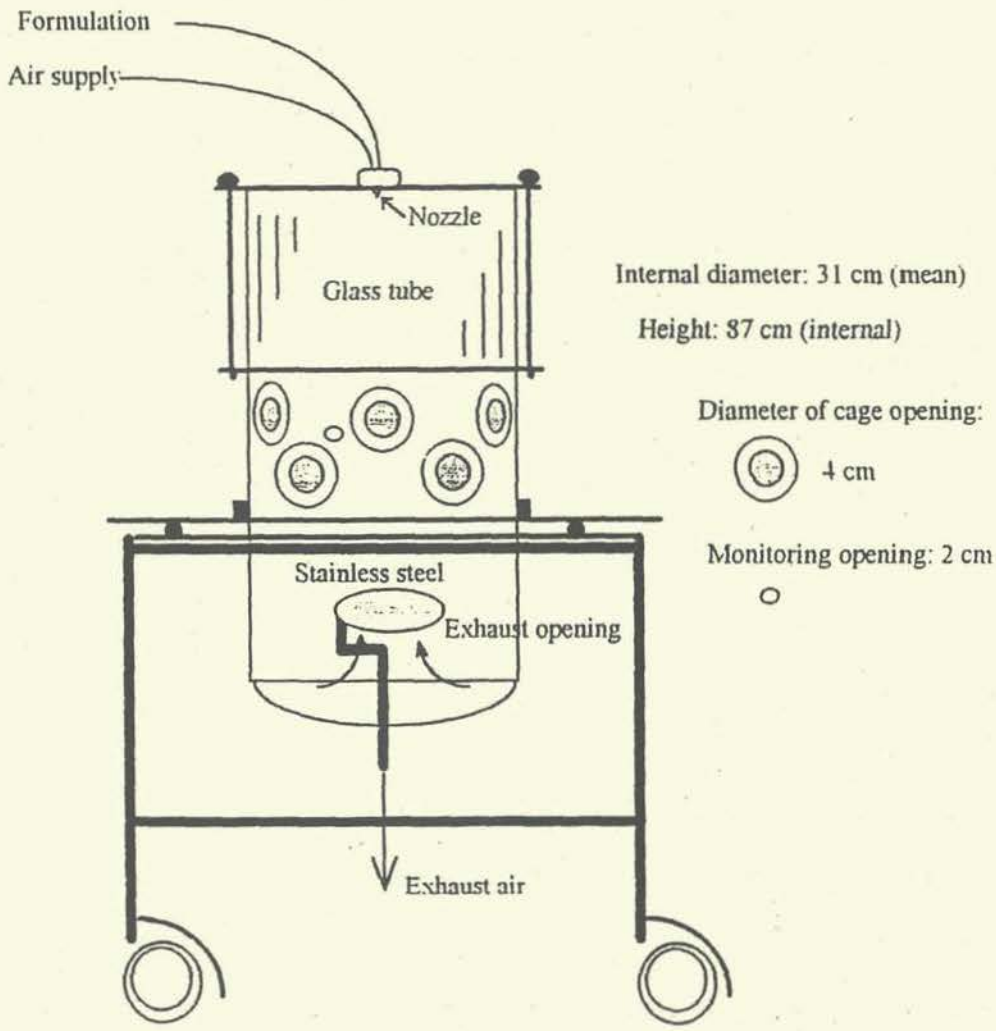
Based on the LD_{50} of >2,000 mg/kg in both sexes of rats, NEU 1140 F was placed in Toxicity Category III.

Report 95 10 42 197
NEU 1140 F/Acute Inhalation Toxicity

BioChem

Figure 1

Inhalation chamber



I. MATERIALS

A. Test Material:

Chemical Name: Copper Octanoate
Synonym: NEU 1140 F
Purity: 10% copper fatty acids
Batch Number: 03/03
Description: Turquoise liquid
Storage Conditions: At room temperature in the dark

The dosing solution was applied undiluted. Dose-volumes were determined based on the body weight of the individual animal and administered at a dose volume of 1.91 ml/kg.

B. Test Animals:

Species: Rat
Strain: Wistar Crl:(WI) BR
Source: Charles River, Germany
Age: Approx. 8 weeks
Weight: Males - 246 to 290 g; Females - 218 to 227 before dosing
Housing: Individually housed in polycarbonate cage
Environmental Conditions: Temperature: 21°C
Relative Humidity: 50%
Photoperiod: 12 hours light/dark
Air Changes: 15/hour
Food and Water: Standard Pelleted Laboratory Animal diet (Carfil quality BVBA, Oud-Turnhout, Belgium) and water *ad libitum*
Acclimation Period: At least five days

II. STUDY DESIGN AND METHODS:

No rationale for the selection of dose level was reported. In the main study, one day prior to dosing, an area of approximately 5x7 cm on the back of each of five males and five females was clipped, exposing an area of approximately 10% of the total body surface. On the day of dosing, 2,000 mg/kg of test material was applied to the shaved area (5x5 cm for males; 3.5x5 cm for females). The amount of test substance/area covered approximately 10% of the body surface area. The treated area was covered with a gauze patch and held in place with a flexible bandage. Twenty-four hours after the application, the treated skin was washed with a tissue moistened with tap water before

assessing the skin reaction. The animals were observed for occurrence of mortality twice daily as well as for clinical signs of toxicity on the day of dosing and once daily for the remainder of the 15-day observation period. Body weights were recorded prior to dosing, and at 8 and 15 days post-dosing. At the end of observation period, all animals were sacrificed and necropsied.

II. RESULTS AND DISCUSSION:

No mortalities occurred during the 15-day observation period. No clinical signs of toxicity were noted after treatment and throughout the 15-day observation period. Body weights were unaffected by the treatmwent. Upon necropsy, no abnormalities were noted. **The acute dermal LD_{50} for both sexes of rabbits was greater than 2,000 g/kg.**

III. CONCLUSIONS

Based on the acute dermal LD_{50} of >2000 mg/kg in male and female rabbits, NEU 1140 F was placed in Toxicity Category III.

Copper Octanoate Acute Inhalation Study (§81-3)

Reviewed by: Sanjivani B. Diwan, Ph.D. Sanjivani B. Diwan Date: 2/25/97
Review Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Alan C. Levy, Ph.D., Alan C. Levy, Date: 2/25/97
Review Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Acute Inhalation Toxicity/Rats OPPTS 870.1300 [§81-3]
DP BARCODE: D230195	SUBMISSION NO.: S511757
P. C. CODE: 023306	MRID NUMBER: 43970201
TEST MATERIAL (PURITY):	Copper Octanoate (10% copper fatty acids)
SYNONYM:	NEU 1140 F
CITATION:	Grunert, B. 1996. 4-Hour Acute Inhalation Toxicity Study with NEU 1140 F in Rats BioChem GmbH Daimlerstrabe 5b, Karlsruhe, Germany; NOTOX Project Report 95 10 42 197. January 19, 1996
SPONSOR:	Neudorff GmbH KG, D-31860 Emmerthal, Germany

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID # 43970201), groups of five male and five female Sprague-Dawley rats were exposed to aerosol concentration of 0.38 mg/L NEU 1140 F for four hours. The animals were observed for mortality and clinical signs of toxicity during the exposure and the 14-day post-exposure observation period.

There were no mortalities and clinical signs observed. The body weights were comparable. On necropsy, no abnormalities were noted. The calculated nominal and measured concentrations of the test material for the four-hour exposure were 5.0 and 0.38 mg/L, respectively. The mean MMADs ranged between 0.553-0.554 μm (GSD range: 0.540-0.541 μm) with 98.6% of the sampled particles <3 μm in size. **Based on the lack of mortality and clinical signs, an acute inhalation LC_{50} was considered to be >0.38 mg/L (the highest achievable concentration)in both sexes of rats, NEU 1140 F was placed in Toxicity Category III.**

This study is classified as Acceptable and satisfies the requirements (81-3) for an acute inhalation study in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided. No Flagging statement was provided.

I. MATERIALS

A. Test Material

Chemical Name: Copper Octanoate
Synonym: NEU 1140 F
Purity: 10% copper fatty acids
Batch Number: Not reported
Description: Turquoise blue liquid
Storage Conditions: Not reported

An aerosol containing 5 mg test formulation per liter air was generated for inhalation. Food and water were held during exposure.

B. Test Animals

Species: Rat
Strain: Sprague-Dawley albino
Source: Interfauna, Germany
Age: Not stated
Weight: Males - 187-210 g; Females - 180-189 g before dosing
Housing: Individually in Macrolon cages
Environmental Conditions: Temperature: 19-23°C
Relative Humidity: 30-70%
Photoperiod: 12 hours light/dark
Air Changes: 15/hour
Food and Water: Haltungsdiat "ALMA 0801 H 1003" diet, 8 g twice daily and water *ad libitum*
Acclimation Period: Five days

II. STUDY AND METHODS

Exposure Chamber

The SIT 3000 whole-body exposure chamber had a diameter of 31 cm and an internal height of 87 cm with a calculated volume of 65.7 liters.

Atmosphere Generation and Monitoring

A stationary flow of 15 L aerosol/min was maintained by using 5 mg formulation per liter aerosol or the highest technical achievable test substance concentration over 4-hour exposure period. The test concentration was generated as follows: NEU 1140 F formulation (45 g) was added to a

volumetric flask (500 ml capacity); 22.6 g of polyethylene glycol PEG 400 was added as a stabilizer to maintain the aerosol particle distribution in the needed range. The deionized water was added to fill the volume of the flask. The 200 ml of test solution containing 18 g of NEU 1140 F formulation and 9 g PEG 400 was distributed into the chamber over 4 hours exposure. The higher concentrations of the test substance precipitated clogging up the nozzle within a short time. The highest achievable concentration was 0.38 mg/L. The test aerosol was generated by the nozzle at the top of exposure chamber and distributed to all cage openings where it was delivered to the animals (head-nose-exposure only). The exhaust outlet at the bottom of the chamber was maintained under a slightly negative pressure.

A diagram of the exposure chamber is attached to the DER.

During 4-hour exposure period, samples of the test atmosphere were drawn. During 30-minute sampling time, the airflow was maintained at 2.5 l/min resulting in 75 l air which sucked through water filled washing bottles. After sampling the air flow was discontinued from the chamber, rinsed with water into the washing bottles. The concentration of the test aerosol in the entire water sample was determined.

The nominal concentration of the test atmosphere was calculated from the concentration of the test solution and the amount of test solution pumped into the chamber.

The particle size distribution of the test atmosphere was determined three times during the exposure period using a Palas particle counter/sizer PCS 2000 combined with a 1:10 diluting stage Palas® VKL 10. The mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the particles were calculated.

Air flow rate from the chamber, temperature, relative humidity, and percent oxygen content were monitored during the exposure at the site of the animals's snout.

Animal Treatment

Groups of five male and five female rats received a "Head-Nose-Exposure only" at gravimetric concentrations of 0.38 mg/l. Observations for mortality, clinical signs, and body weight were made during observation period of 15 days (frequency not reported). At the end of the study, all the surviving animals were sacrificed and necropsied. LC_{50} values were calculated.

II. RESULTS

Test Atmosphere

The calculated nominal concentration of the test material for the four exposure groups was 5.0 mg/l. The respective mean gravimetric concentration was 0.38 mg/L and the mean MMADs ranged between 0.553-0.554 μm (GSD range: 0.540-0.541 μm) with 98.6% of the sampled particles <3 μm in size..

The mean chamber temperature and relative humidity ranged from 21.9–23.6^0 C and 90–102%, respectively. Oxygen content was at 21% and the air flow rate was 15 L/minute. The theoretical time required for the chamber to reach saturation of the inhalation chamber was 8 minutes .

No deaths occurred during exposure or observation period at exposure concentration of 0.38 mg/L. There were no clinical signs observed during 14-day observation period. The body weights were unaffected by the treatment and no microscopic abnormalities were noted.

III. CONCLUSIONS

Based on the acute inhalation LC_{50} of >0.38 mg/L in both sexes of rats, NEU 1140 F was placed in Toxicity Category III.

Copper Octanoate Primary Eye Irritation Study (§81-5)

Reviewed by: Sanjivani B. Diwan, Ph.D Sanjivani B Diwan, Date: 2/25/97
Review Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Alan C. Levy, Ph.D., Alan C. Levy, Date: 2/25/97
Review Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Primary Eye Irritation- Rabbits OPPTS 870.2400 [§81-4]
DP BARCODE: D230195 P. C. CODE: 023306	SUBMISSION NO.: S511757 MRID NUMBER: 43947506
TEST MATERIAL (PURITY):	Copper Octanoate (10% copper fatty acids)
SYNONYM:	NEU1140F
CITATION:	Pels Rijcken W.R. 1995. Acute Eye Irritation/Corrosion Study with NEU 1140 F in the Rabbit. NOTOX Hambakenwetering 3, 5203 DL's-Hertogenbosch, Netherlands; NOTOX Project 154834. September 28, 1995
SPONSOR:	Neudorff GmbH KG, D-31860 Emmerthal, Germany

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID # 43947506), 0.1 ml of NEU1140F (10% copper fatty acids) instilled into the conjunctival sac of one eye of each of three male New Zealand white rabbits. The other eye served as an untreated control. The eyes were examined for signs of irritation and scored at 1, 24, 48 and 72 hours post-dosing. The treated and untreated eyes were observed at 24 hours following instillation of an aqueous 2% fluorescein solution. Application of NEU1140F caused irritation of conjunctivae in all rabbits which was reversible within 48 hours. **The study demonstrated that NEU1140F produces transient ocular irritation in rabbits. NEU1140F was therefore, placed in Toxicity Category IV.**

This study is classified as **Acceptable** and **satisfies** the requirements (81-4) for a primary eye irritation study in rabbits.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided. No Flagging statement was provided.

I. MATERIALS

A. Test Material

Chemical Name: Copper Octanoate
Synonym: NEU1140F;
Purity: 10% copper fatty acids
Batch Number: 03/03
Description: Turquoise liquid
Storage Conditions: At room temperature in the dark

The test material was applied undiluted into the conjunctival sac of one eye of each animal while the other eye served as control.

B. Test Animals

Species: Rabbit
Strain: New Zealand white
Source: Broekman Institute, Someren, Netherlands
Age: Approximatelt 7 weeks
Weight: Males - 1465–1581 g at arrival
Housing: Individually in stainless steel cages
Environmental Conditions: Temperature: 21°C
Relative Humidity: 50%
Photoperiod: 12 hours light
Air Changes: 15/hour
Food and Water: Approx. 100 mg/day standard laboratory rabbit diet, LKK-20 and water *ad libitum*
Acclimation Period: At least five days

II. METHODS

Twenty-four hours prior to dosing, the eyes of rabbits were examined. On the day of dosing, 0.1 ml of the undiluted test material was instilled in to the conjunctival sac of one eye of each animal. The other eye served as an untreated control. After 24 hours, an aqueous solution of 2% fluorescein was instilled into both eyes of each animal to determine the corneal epithelial damage. The eyes were examined for evidence of irritation and scored at 1, 24, 48 and 72 hours using Draize scale.

III. RESULTS

Treatment with copper octanoate resulted in transient corneal irritation in all three rabbits. It consisted of redness of eyelids (Grade 2) in all three rabbits while chemosis of eyelids (Grade 2) or of eyelids, nictitating membrane and sclera (Grade 1) was noted in two rabbits. In addition, all three rabbits had ocular discharge. These symptoms disappeared by 48 hours in all rabbits. The calculated maximum Draize score was 9.3. The study demonstrated that NEU 1140F produced minimal, transient ocular irritation in rabbits.

IV. CONCLUSIONS

The study demonstrated that NEU1140F produced minimal, transient ocular irritation in rabbits. NEU 1140F, therefore, was placed in Toxicity Category IV.

Copper Octanoate Primary Dermal Irritation Study (§81-5)

Reviewed by: Sanjivani B. Diwan, Ph.D. Sanjivani B. Diwan, Date: 2/25/97
Review Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Alan C. Levy, Ph.D.. Alan C. Levy, Date: 2/25/97
Review Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Primary Dermal Irritation- Rabbits
OPPTS 870.2400 (§81-5)

DP BARCODE: D230195
P. C. CODE: 023306

SUBMISSION NO.: S511757
MRID NUMBER: 43947507

TEST MATERIAL (PURITY): Copper Octanoate (10% copper fatty acids)

SYNONYM: NEU1140F

CITATION: Pels Rijcken W.R. 1995. Primary Skin Irritation/Corrosion Study with NEU 1140 F in the Rabbit (4-Hour Semi-Occlusive Application) OTOX Hambakenwetering 3, 5203 DL's-Hertogenbosch, Netherlands; NOTOX Project 154823. September 28, 1995

SPONSOR: Neudorff GmbH KG, D-31860 Emmerthal, Germany

REPORT ISSUED: September 28, 1995

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID # 43947507), 0.5 g of NEU 1140 F (10% copper fatty acids) moistened with 0.5 ml of distilled water was topically applied to a clipped skin area (10 x 15 cm) of each of three male New Zealand white rabbits for four hours. The treated areas were examined for signs of dermal irritation (edema and erythema) and scored at 1, 24, 48 and 72 hours post-treatment. A slight erythema and edema were noted in three and one rabbits, respectively; at 24 hours, erythema was noted in only one rabbit which did not persist up to 72 hours. No systemic signs of toxicity were observed. **The study demonstrated that NEU 1140 F was non-irritating to the rabbit skin. Therefore, NUE 1140 F was placed in Toxicity Category IV.**

The study is classified as **Acceptable** and **satisfies** the requirements (81-5) for a primary dermal irritation study in rabbits.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided. No Flagging statement was provided.

I. MATERIALS

A. Test Material

Chemical Name: Copper Octanoate
Synonym: NEU 1140 F
Purity: 10% copper fatty acids
Batch Number: 03/03
Description: Turquoise liquid
Storage Conditions: At room temperature in the dark

B. Test Animals

Species: Rabbit
Strain: New Zealand white
Source: Broekman Institute, Someren, Netherlands.
Age: Approximately 8 or 10 weeks
Weight: Males - 1370 to 1554 g upon arrival
Housing: Individually in stainless steel cages
Environmental Conditions: Temperature: 21°C
Relative Humidity: 50%
Photoperiod: 12 hours light/dark
Air Changes: 15/hour
Food and Water: Approx. 100 g/day standard laboratory rabbit diet, LKK-20 and water *ad libitum*
Acclimation Period: At least 5 days

II. METHODS

Approximately 24 hours before treatment, the dorsal fur of each rabbit was clipped exposing an area of approximately 150 cm^2 (10 cm x 15 cm). On the day of dosing, 0.5 ml of the test material was applied to the clipped area on one flank. A similar patch was applied to the other flank to serve as a procedural control. Each test area was covered with a gauze mounted on a Micropore tape, wrapped around the abdomen and secured in place with Coban elastic bandage. At the end of the 4-hour exposure, the bandages were removed and the residual test material was wiped off with a tissue moistened with tap-water and a dry tissue. The areas were examined for signs of dermal irritation and scored at 1, 24, 48 and 72 hours post-dosing using Draize scale as follows:

Primary Irritation Index	Degree of Irritation
0	Non-irritating
>0-0.4	Negligibly irritating
>0.4-2.0	Mildly irritating
>2.0-5.0	Modertely irritating
>5.0-8.0	Severely irritating

III. RESULTS

Edema was observed in one of three rabbits and a slight erythema was noted in all three treated rabbits; in one animal erythema lasted up to 24 hours. No signs of systemic toxicity were observed in the treated rabbits at 24, 48 and 72 hours. The promary iritation index was 0.2. The study demonstrated that NEU 1140 F was non-irritating to the rabbit skin.

III. CONCLUSIONS

The study demonstrated that NEU 1140 F (10% copper fatty acids) produces no dermal irritation in rabbits. NEU 1140 F was therefore, placed in Toxicity Category IV.

Copper Octanoate Dermal Sensitization Study (81-6)

Reviewed by: Sanjivani B. Diwan, Ph.D. Sanjivani B. Diwan, Date: 2/25/97
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Alan C. Levy, Ph.D. Alan C. Levy, Date: 2/25/97
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Dermal Sensitization-Guinea Pigs
OPPTS 870.2600 (§81-6)

DP BARCODE: D230195
P. C. CODE: 023306

SUBMISSION NO.: S511757
MRID NUMBER: 44116101

TEST MATERIAL (PURITY): Copper Octanoate (10% copper fatty acids)

SYNONYM: NEU 1140 F

CITATION: Pels Rijcken W.R. 1996. Assessment of Contact Hypersensitivity to NEU 1140 F in the Albino Guinea Pig (Maximization Test). NOTOX, Hambakenwetering 3, 5203 DL's-Hertogenbosch, Netherlands; NOTOX Project 171271. July 30, 1996

SPONSOR: Neudorff GmbH KG, D-31860 Emmerthal, Germany

REPORT ISSUED: July 30, 1996

EXECUTIVE SUMMARY: In a dermal sensitization Maximization Test (MRID # 44116101), twenty female Himalayan albino guinea pigs received three intradermal injections of 0.5% NEU 1140 F in distilled water and one week later an epidermal application of undiluted test material during induction phase. Twenty-two days following the last induction dose, a challenge topical dose at 50% test substance concentration in distilled water was administered to animals. The control group (ten females) was treated only during the challenge phase.

The positive control group received 5% alpha-hexylcinnamicaldehyde (HCA) in distilled water and undiluted (alpha-HCA) during induction phase and 50% alpha-HCA during challenge phase. HCA was a strong sensitizer and induced positive response in all ten animals.

Application of NEU 1140 F produced only slight erythema (Grade 1 reaction) in one test and one control animals after challenge application.

The results of this study indicate that NEU 1140 F is a non-sensitizer of skin in female guinea pigs.

This study is classified as **Acceptable** and **satisfies** the requirements (81-6) for a dermal sensitization study in guinea pigs.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided. No Flagging statement was provided.

I. MATERIALS

A. Test Material

Chemical Name: Copper Octanoate
Synonym: NEU 1140 F
Purity: 10% copper fatty acids
Batch Number: 03/03
Description: Turquoise liquid
Storage Conditions: At room temperature in the dark

The dosing solution was administered undiluted in the clipped flank area. Dose-volumes were determined based on the body weight of the individual animal and administered at a dose volume of 1.90 ml/kg.

B. Test Animals

Species: Guinea pigs
Strain: Albino, Himalayan strain
Source: BRL Ltd., Basel, Switzerland
Age: Approx. 5 weeks
Weight: Males and Females - maximum 500 g on day 1
Housing: Five per cages
Food and water: Standard guinea pig diet containing 1600 mg/kg ascorbic acid and tap water *ad libitum*
Environmental Conditions: Temperature: 21°C
Relative Humidity: 50%
Photoperiod: 12 hours light/dark
Air Changes: 15/hour
Acclimation Period: At least five days

II. METHODS

The study was conducted using Maximization test. The animals were assigned to four groups as summarized below.

Group	# Females	Induction Dose Concentration[a]	Challenge Dose Concentration
NEU 1140 F	10	0.5%[b]; neat[b]	50%
Control	10	- -	50%
Alpha-HCA[c,d]	10	5%[b]; neat[b]	50%

[a]The test substance concentrations were selected based on the results of preliminary study in which, 50-100% NEU 1140 F in distilled water was found to be non-sensitizing to guinea pig skin.
[b]Intradermal injections of 0.5% and epidermal application of neat material
[c]Intradermal injections of 5% and epidermal application of neat material
[d]Experiment for positive control group was conducted separately.

MAIN STUDY

Induction Phase

During intradermal induction, three pairs of injections (0.1 ml/site) were made in the clipped flank area as follows:

Test group animals received two injections each of Freund's adjuvant/water (50:50) in the front row; 2 injections each of test substance at 0.5% concentration in distilled water in the middle row; and 2 injections each at 1.0% concentration of test substance emulsified in a 50:50 mixture of Freund's Complete Adjuvant in the back row. Control animals received similar injections with formulating agent but without the test substance. Skin reactions were recorded 2 days after the beginning the intradermal induction phase.

During percutaneous induction phase (one week after intradermal induction), the scapular area between the injection sites was clipped and treated with 0.5 ml of undiluted test substance for 48 hours using a Scotchpak-non-woven patch (2x3 cm) mounted on Micropore tape and secured with Coban elastic bandage. Evaluations for signs of dermal irritation were made at 48 hours post-application.

Challenge Phase

Twenty-two days following the last induction dose, the challenge doses of the test and control chemicals were applied to the test sites. The following procedure was used:

An occluded topical application of 50% test substance concentration and the vehicle (0.5 ml each), using Scotchpak-non-woven patch (2x3 cm) mounted on Micropore tape and secured with Coban elastic bandage. Control group received vehicle only. Twenty-four hours later, residual test material was removed from the test site and the skin reactions were assessed at 24 and 48 hours.

The test material was considered a potential human skin sensitizer if a positive response (Grade 1 or above) was seen in animals; for sensitization rate refer to table below.

Sensitization Rate	Grade	Classification
0		Non
>0-8	I	Weak
9-28	II	Mild
29-64	III	Moderate
65-80	IV	Strong
81-100	V	Extreme

Animals were observed for mortality twice daily and for clinical signs at least once daily. The body weights of animals were determined at initiation and termination of the study.

III. RESULTS

Following intradermal injection with 0.5% test concentration, signs of necrosis were noted in all test animals. Slight erythema in 6 animals and severe erythema (Grade 3) in one animal were noted after epidermal injection of 0.5% NEU 1140 F during induction period. Twenty-four hours following challenge application, two animals, one control and one treated, developed slight erythema (Grade 1); two of the treated animals including one with slight erythema exhibited signs of necrosis in approximately 25% of the application area after 24 hours. These were attributed to scratching by the animals. No adverse effects of NEU 1140 F on body weights were noted.

At 24 and 48 hours after challenge application with 50% alpha-HCA, mild (Grade 2) to strong skin reactions (Grade 4) were observed in 100 % of positive control animals.

IV. CONCLUSIONS

The results indicate that NEU 1140 F is a non-sensitizer of skin in female guinea pigs.